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Dated 26 June 2003

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10SEP02 E747168-7 D00019
P01/7700 0.00-0220961.7

Request for grant of a patent

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The Patent Office

Cardiff Road
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1. Your reference

P031735GB

2. Patent application number
(The Patent Office will fill in this part)

10 SEP 2002

0220961.7

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

BAYER AG
D-51368 LEVERKUSEN
GERMANY

Patents ADP number *(if you know it)* 08100414001

If the applicant is a corporate body, give the country/state of its incorporation

GERMANY

4. Title of the invention

HETEROCYCLIC DERIVATIVES

5. Name of your agent *(if you have one)*

Carpmaels & Ransford

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

43 Bloomsbury Square
London
WC1A 2RA

Patents ADP number *(if you know it)*

83001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) *any applicant named in part 3 is not an inventor, or*
b) *there is an inventor who is not named as an applicant, or*
c) *any named applicant is a corporate body*

See note (d))

Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	-
Description	42
Claim(s)	10
Abstract	1
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item.

Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	- -

11. I/We request the grant of a patent on the basis of this application.

Signature: Carpmaels & Ransford — Date: **10th September 2002**

Carpmaels & Ransford

12. Name and daytime telephone number of person to contact in the United Kingdom: **ADRIAN FISHER** **020-7242 8692**

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Notes

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Heterocyclic derivatives

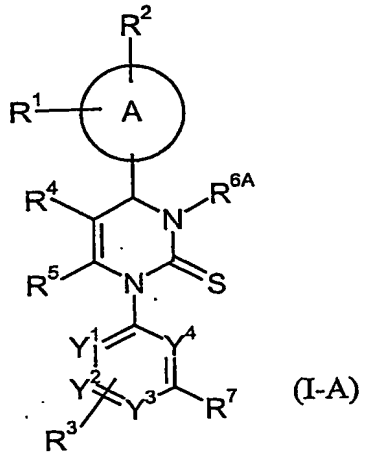
The present invention relates to novel heterocyclic derivatives, processes for their preparation, and their use in medicaments, especially for the treatment of chronic obstructive pulmonary diseases.

The fibrous protein elastin, which comprises an appreciable percentage of all protein content in some tissues, such as the arteries, some ligaments and the lungs, can be hydrolysed or otherwise destroyed by a select group of enzymes classified as elastases. Human leukocyte elastase (HLE, EC 3.4.21.37), also known as human neutrophil elastase (HNE), is a glycosylated, strongly basic serine protease and is found in the azurophilic granules of human polymorphonuclear leukocytes (PMN). HNE is released from activated PMN and has been implicated causally in the pathogenesis of acute and chronic inflammatory diseases. HNE is capable of degrading a wide range of matrix proteins including elastin, and in addition to these actions on connective tissue HNE has a broad range of inflammatory actions including upregulation of IL-8 gene expression, oedema formation, mucus gland hyperplasia and mucus hypersecretion. Pulmonary diseases where HNE is believed to play a role include lung fibrosis, pneumonia, acute respiratory distress syndrome (ARDS), pulmonary emphysema, including smoking-induced emphysema, chronic obstructive pulmonary diseases (COPD) and cystic fibrosis. HNE has also been causally implicated in rheumatoid arthritis, atherosclerosis, brain trauma, cancer and related conditions in which neutrophil participation is involved. Thus, inhibitors of HLE activity can be potentially useful in the treatment of a number of inflammatory diseases, especially of chronic obstructive pulmonary diseases [R.A. Stockley, *Neutrophils and protease/antiprotease imbalance*, Am. J. Respir. Crit. Care 160, S49-S52 (1999)].

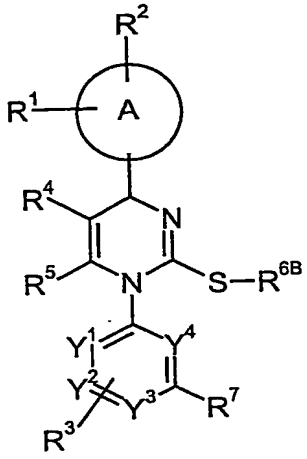
The synthesis of certain 6-methyl-1,4-diphenyl-3,4-dihydro-2(1H)-pyrimidinethione derivatives is described in *J. Comb. Chem.* 3, 624-630 (2001), *J. Fluorine Chem.* 90, 17-21 (1998) and *Khim. Geterotsikl. Soedin.* 9, 1223-1227 (1986) [*Chem. Abstr.* 107,

39737 (1987)]. A specific pharmacological activity of these compounds is not mentioned.

The present invention relates to compounds of the general formulas (I-A) and (I-B)



(I-A)



(I-B),

wherein

A represents an aryl or heteroaryl ring,

R^1, R^2 and R^3 independently from each other represent hydrogen, halogen, nitro, cyano, C_1-C_6-alkyl, hydroxy or C_1-C_6-alkoxy, wherein C_1-C_6-alkyl and C_1-C_6-alkoxy can be further substituted with one to three identical or different radicals selected from the group consisting of halogen, hydroxy and C_1-C_4-alkoxy,

R^4 represents C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, hydroxycarbonyl, aminocarbonyl, mono- or di-C_1-C_4-alkylaminocarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylcarbonyl, heterocyclylcarbonyl, heteroaryl, heterocyclyl or cyano, wherein C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, mono- and di-C_1-C_4-alkylaminocarbonyl can be further substituted with one to three identical or different radicals selected from the group consisting of C_3-C_8-

cycloalkyl, hydroxy, C_1-C_4-alkoxy, C_1-C_4-alkoxycarbonyl, hydroxycarbonyl, aminocarbonyl, mono- and di-C_1-C_4-alkylaminocarbonyl, C_1-C_4-alkylcarbonylamino, amino, mono- and di-C_1-C_4-alkylamino, heteroaryl, heterocyclyl and tri-(C_1-C_6-alkyl)-silyl,

R^5 represents C_1-C_4-alkyl, which can be substituted with one to three identical or different radicals selected from the group consisting of halogen, hydroxy, C_1-C_6-alkoxy, C_1-C_6-alkenoxy, C_1-C_6-alkylthio, amino, mono- and di-C_1-C_6-alkylamino, arylamino, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl and the radical -O-C_1-C_4-alkyl-O-C_1-C_4-alkyl,

R^{6A} represents hydrogen, C_1-C_6-alkylcarbonyl, C_3-C_8-cycloalkylcarbonyl, C_1-C_6-alkoxycarbonyl, mono- or di-C_1-C_4-alkylaminocarbonyl, wherein C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, mono- and di-C_1-C_4-alkylaminocarbonyl can be substituted with one to three identical or different radicals selected from the group consisting of C_3-C_8-cycloalkyl, hydroxy, C_1-C_4-alkoxy, amino, mono- and di-C_1-C_4-alkylamino,

R^{6B} represents C_1-C_6-alkyl, which can be substituted with one to three identical or different radicals selected from the group consisting of hydroxy, C_1-C_4-alkoxy, amino, mono- and di-C_1-C_4-alkylamino, aryl and heteroaryl,

R^7 represents halogen, nitro, cyano, C_1-C_6-alkyl, hydroxy or C_1-C_6-alkoxy, wherein C_1-C_6-alkyl and C_1-C_6-alkoxy can be further substituted with one to three identical or different radicals selected from the group consisting of halogen, hydroxy and C_1-C_4-alkoxy,

and

Y^1, Y^2, Y^3 and Y^4 independently from each other represent CH or N, wherein the ring contains either 0, 1 or 2 nitrogen atoms.

The compounds according to this invention can also be present in the form of their salts, hydrates and/or solvates.

Physiologically acceptable salts are preferred in the context of the present invention.

Physiologically acceptable salts according to the invention are non-toxic salts which in general are accessible by reaction of the compounds (I) with an inorganic or organic base or acid conventionally used for this purpose. Non-limiting examples of pharmaceutically acceptable salts of compounds (I) include the alkali metal salts, e.g. lithium, potassium and sodium salts, the alkaline earth metal salts such as magnesium and calcium salts, the quaternary ammonium salts such as, for example, triethyl ammonium salts, acetates, benzene sulphonates, benzoates, dicarbonates, disulphates, ditartrates, borates, bromides, carbonates, chlorides, citrates, dihydrochlorides, fumarates, gluconates, glutamates, hexyl resorcinates, hydrobromides, hydrochlorides, hydroxynaphthoates, iodides, isothionates, lactates, laurates, malates, maleates, mandelates, mesylates, methylbromides, methylnitrates, methylsulphates, nitrates, oleates, oxalates, palmitates, pantothenates, phosphates, diphosphates, polygalacturonates, salicylates, stearates, sulphates, succinates, tartrates, tosylates, valerates, and other salts used for medicinal purposes.

Hydrates of the compounds of the invention or their salts are stoichiometric compositions of the compounds with water, such as for example hemi-, mono-, or dihydrates.

Solvates of the compounds of the invention or their salts are stoichiometric compositions of the compounds with solvents.

The present invention includes both the individual enantiomers or diastereomers and the corresponding racemates or diastereomeric mixtures of the compounds according to the invention and their respective salts. In addition, all possible tautomeric forms

of the compounds described above are included according to the present invention. The diastereomeric mixtures can be separated into the individual isomers by chromatographic processes. The racemates can be resolved into the respective enantiomers either by chromatographic processes on chiral phases or by resolution.

In the context of the present invention, the substituents, if not stated otherwise, in general have the following meaning:

Alkyl in general represents a straight-chain or branched hydrocarbon radical having 1 to 6, preferably 1 to 4 carbon atoms. Non-limiting examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, hexyl, isohexyl. The same applies to radicals such as alkoxy, alkylamino, alkoxycarbonyl and alkoxycarbonylamino.

Alkoxy illustratively and preferably represents methoxy, ethoxy, n-propoxy, isopropoxy, tert.-butoxy, n-pentoxy and n-hexoxy.

Alkylcarbonyl in general represents a straight-chain or branched hydrocarbon radical having 1 to 6, preferably 1 to 4 carbon atoms which has a carbonyl function at the position of attachment. Non-limiting examples include formyl, acetyl, n-propionyl, n-butyryl, isobutyryl, pivaloyl, n-hexanoyl.

Cycloalkyl in general represents a cyclic saturated hydrocarbon radical having 3 to 8, preferably 3 to 6 carbon atoms. Non-limiting examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Cycloalkylcarbonyl represents a cycloalkyl radical having 3 to 8, preferably 3 to 6 ring carbon atoms which is bound via a carbonyl group, illustratively and preferably representing cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl and cycloheptylcarbonyl.

Alkoxycarbonyl illustratively and preferably represents methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert.-butoxycarbonyl, n-pentoxycarbonyl and n-hexoxycarbonyl.

Alkylamino represents an alkylamino radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylamino, ethylamino, n-propylamino, isopropylamino, tert.-butylamino, n-pentylamino, n-hexylamino, *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-n-propylamino, *N*-isopropyl-*N*-n-propylamino, *N*-tert.-butyl-*N*-methylamino, *N*-ethyl-*N*-n-pentylamino and *N*-n-hexyl-*N*-methylamino.

Alkylaminocarbonyl represents an alkylaminocarbonyl radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, tert.-butylaminocarbonyl, n-pentylaminocarbonyl, n-hexylaminocarbonyl, *N,N*-dimethylaminocarbonyl, *N,N*-diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-methyl-*N*-n-propylaminocarbonyl, *N*-isopropyl-*N*-n-propylaminocarbonyl, *N*-tert.-butyl-*N*-methylaminocarbonyl, *N*-ethyl-*N*-n-pentylamino-carbonyl and *N*-n-hexyl-*N*-methylaminocarbonyl.

Aryl represents a mono- to tricyclic aromatic carbocyclic radical having generally 6 to 14 carbon atoms, illustratively and preferably representing phenyl, naphthyl and phenanthrenyl.

Heteroaryl per se and in heteroarylcarbonyl represents an aromatic mono- or bicyclic radical having generally 5 to 10 and preferably 5 or 6 ring atoms and up to 5 and preferably up to 4 heteroatoms selected from the group consisting of S, O and N, illustratively and preferably representing thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyridyl, pyrimidyl, pyridazinyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl.

Heteroarylcarbonyl illustratively and preferably represents thienylcarbonyl, furylcarbonyl, pyrrolylcarbonyl, thiazolylcarbonyl, oxazolylcarbonyl, imidazolyl-carbonyl, pyridylcarbonyl, pyrimidylcarbonyl, pyridazinylcarbonyl, indolylcarbonyl, indazolylcarbonyl, benzofuranylcarbonyl, benzothiophenylcarbonyl, quinolinyl-carbonyl, isoquinolinylcarbonyl.

Heterocyclyl per se and in heterocyclylcarbonyl represents a mono- or polycyclic, preferably mono- or bicyclic, nonaromatic heterocyclic radical having generally 4 to 10 and preferably 5 to 8 ring atoms and up to 3 and preferably up to 2 heteroatoms and/or hetero groups selected from the group consisting of N, O, S, SO and SO_2. The heterocyclyl radicals can be saturated or partially unsaturated. Preference is given to 5- to 8-membered monocyclic saturated heterocyclyl radicals having up to two heteroatoms selected from the group consisting of O, N and S, such as illustratively and preferably tetrahydrofuran-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, piperidinyl, morpholinyl, perhydroazepinyl.

Heterocyclylcarbonyl illustratively and preferably represents tetrahydrofuran-2-carbonyl, pyrrolidine-2-carbonyl, pyrrolidine-3-carbonyl, pyrrolinecarbonyl, piperidinecarbonyl, morpholinecarbonyl, perhydroazepinecarbonyl.

Halogen represents fluorine, chlorine, bromine and iodine.

When stated, that Y^1, Y^2, Y^3 and Y^4 represent CH or N, CH shall also stand for a ring carbon atom, which is substituted with a substituent R^3.

In another embodiment, the present invention relates to compounds of general formulas (I-A) and (I-B),

wherein

A represents a phenyl or pyridyl ring,

R^1, R^2 and R^3 independently from each other represent hydrogen, fluoro, chloro, bromo, nitro, cyano, methyl, ethyl, trifluoromethyl or trifluoromethoxy,

R^4 represents C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, hydroxycarbonyl, aminocarbonyl, mono- or di-C_1-C_4-alkylaminocarbonyl or cyano, wherein C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl and mono-C_1-C_4-alkylamino-carbonyl can be substituted with one to three identical or different radicals selected from the group consisting of C_3-C_6-cycloalkyl, hydroxy, C_1-C_4-alkoxy, C_1-C_4-alkoxycarbonyl, amino, mono- or di-C_1-C_4-alkylamino, heteroaryl and heterocyclyl,

R^5 represents methyl or ethyl,

R^{6A} represents hydrogen, C_1-C_6-alkylcarbonyl or C_3-C_6-cycloalkylcarbonyl, wherein C_1-C_6-alkylcarbonyl can be substituted with a radical selected from the group consisting of C_3-C_6-cycloalkyl, hydroxy, C_1-C_4-alkoxy, amino, mono- and di-C_1-C_4-alkylamino,

R^{6B} represents C_1-C_6-alkyl, which can be substituted with a radical selected from the group consisting of hydroxy, C_1-C_4-alkoxy, amino, mono- and di-C_1-C_4-alkylamino, phenyl and heteroaryl,

R^7 represents halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, methyl or ethyl,

and

Y^1, Y^2, Y^3 and Y^4 each represent CH.

In another embodiment, the present invention relates to compounds of general formulas (I-A) and (I-B),

wherein

A represents a phenyl or a pyridyl ring,

R^1 and R^3 each represent hydrogen,

R^2 represents fluoro, chloro, bromo, nitro or cyano,

R^4 represents C_1-C_4-alkylcarbonyl or C_1-C_4-alkoxycarbonyl, wherein C_1-C_4-alkoxycarbonyl can be substituted with a radical selected from the group consisting of hydroxy, C_1-C_4-alkoxy, C_1-C_4-alkoxycarbonyl, mono- and di-C_1-C_4-alkylamino, heteroaryl and heterocyclyl,

R^5 represents methyl,

R^{6A} represents hydrogen, C_1-C_6-alkylcarbonyl or C_3-C_6-cycloalkylcarbonyl,

R^{6B} represents C_1-C_4-alkyl, which can be substituted with a radical selected from the group consisting of hydroxy, C_1-C_4-alkoxy, amino, di-C_1-C_4-alkylamino, phenyl, pyridyl and imidazolyl,

R^7 represents trifluoromethyl or nitro,

and

Y^1, Y^2, Y^3 and Y^4 each represent CH.

In another embodiment, the present invention relates to compounds according to general formulas (I-A) and (I-B), wherein A is phenyl or pyridyl.

In another embodiment, the present invention relates to compounds according to general formulas (I-A) and (I-B), wherein R^1 is hydrogen.

In another embodiment, the present invention relates to compounds according to general formulas (I-A) and (I-B), wherein R^2 is cyano, especially wherein A is phenyl or pyridyl and R^2 is cyano located in para-position relative to the central dihydropyrimidinthione ring.

In another embodiment, the present invention relates to compounds according to general formulas (I-A) and (I-B), wherein R^3 is hydrogen.

In another embodiment, the present invention relates to compounds according to general formulas (I-A) and (I-B), wherein R^4 is C_1-C_4-alkoxycarbonyl or C_1-C_4-alkylcarbonyl, especially methylcarbonyl.

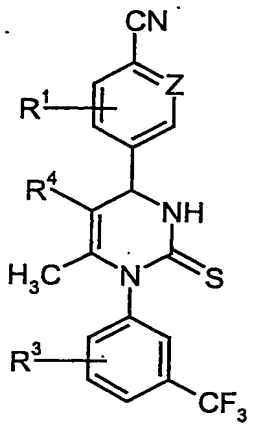
In another embodiment, the present invention relates to compounds according to general formulas (I-A) and (I-B), wherein R^5 is methyl.

In another embodiment, the present invention relates to compounds according to general formula (I-A), wherein R^{6A} is hydrogen.

In another embodiment, the present invention relates to compounds according to general formula (I-B), wherein R^{6B} is methyl, (1H-imidazol-2-yl)methyl or 2-(diethylamino)ethyl.

In another embodiment, the present invention relates to compounds according to general formulas (I-A) and (I-B), wherein R^7 is trifluoromethyl or nitro.

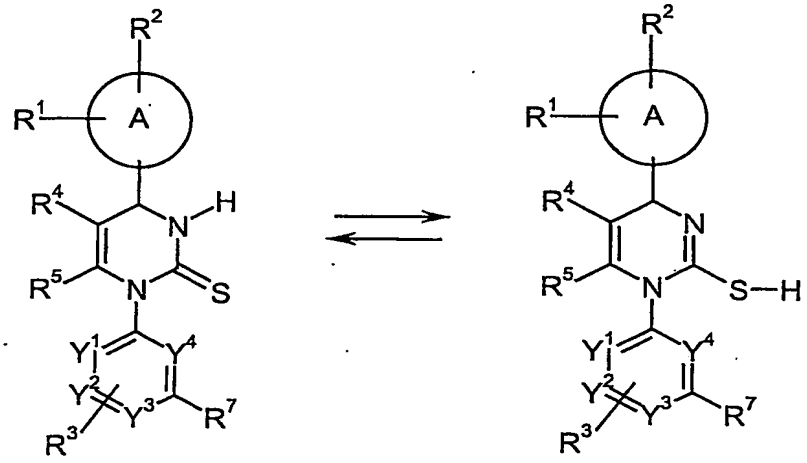
In another embodiment, the present invention relates to compounds of general formula (I-C)



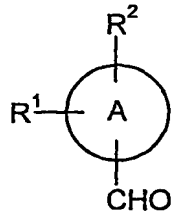
(I-C),

wherein Z represents CH or N, and R^1, R^3 and R^4 have the meaning indicated above.

The compounds of the present invention, wherein R^{6A} in general formula (I-A) is hydrogen, can enolize into the corresponding mercaptoamidines:



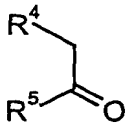
The compounds of general formulas (I-A) and (I-B) can be synthesized by condensing compounds of general formula (II)



(II),

wherein A, R^1 and R^2 have the meaning indicated above,

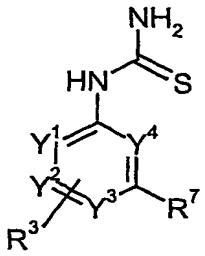
with compounds of general formula (III)



(III),

wherein R^4 and R^5 have the meaning indicated above,

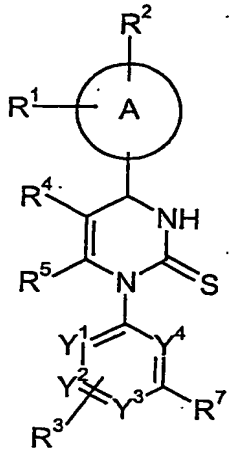
and compounds of general formula (IV)



(IV),

wherein R^3, R^7, and Y^1 to Y^4 have the meaning indicated above,

in the presence of an acid either in a three-component / one-step reaction or sequentially to give compounds of the general formula (I-D)



(I-D),

wherein A, R^1 to R^5, R^7, and Y^1 to Y^4 have the meaning indicated above,

optionally followed by reaction of the compounds of general formula (I-D) in the presence of a base either

[A] with compounds of the general formula (V)

$$R^{6A*}-X^A \quad (V),$$

wherein R^{6A*} has the meaning of R^{6A} as indicated above, but does not represent hydrogen, and X^A represents a leaving group, such as halogen,

to give compounds of the general formula (I-A),

or

[B] with compounds of the general formula (VI)

$$R^{6B}-X^B \quad (VI),$$

wherein R^{6B} has the meaning indicated above and X^B represents a leaving group, such as halogen, tosylate, mesylate or sulfate,

to give compounds of the general formula (I-B).

Suitable solvents for the process (II) + (III) + (IV) → (I-D) are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, diisopropyl ether, 1,2-dimethoxyethane, dioxan or tetrahydrofuran, ethyl acetate, acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, or alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or t-butanol, or hydrocarbons such as pentane, hexane, cyclohexane, benzene, toluene or xylene, or halogeno-hydrocarbons such as dichloromethane, dichloroethane, trichloromethane or chlorobenzene. It is also possible to use mixtures of the above-mentioned solvents. Preferred for the process is tetrahydrofuran.

Suitable acids for the process (II) + (III) + (IV) → (I-D) are generally inorganic or organic acids. These preferably include carboxylic acids, such as, for example, acetic acid or trifluoroacetic acid, sulfonic acids, such as, for example, methanesulfonic acid or p-toluenesulfonic acid, hydrochloric acid or phosphoric acids such as polyphosphoric acids. Preference is given to polyphosphoric acid ethyl ester or polyphosphoric acid trimethylsilyl ester. The acid is employed in an amount from 0.25 mol to 100 mol, relative to 1 mol of the compound of the general formula (III).

The process is in general carried out in a temperature range from +20°C to +150°C, preferably from +60°C to +100°C.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

Suitable solvents for the process (I-D) + (V) → (I-A) are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, diisopropyl ether, 1,2-dimethoxyethane, dioxan or tetrahydrofuran, ethyl acetate, acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, or halogeno-hydrocarbons such as dichloromethane, dichloroethane, trichloromethane or chlorobenzene. It is also possible to use mixtures of the abovementioned solvents. Preferred for the process is tetrahydrofuran.

Suitable bases for the process (I-D) + (V) → (I-A) are generally inorganic or organic bases. These preferably include cyclic amines, such as, for example, piperidine, pyridine or 4-N,N-dimethylaminopyridine, or (C_1-C_4)-trialkylamines, such as, for example, triethylamine or diisopropylethylamine. Preference is given to pyridine. The base is employed in an amount from 0.1 mol to 10 mol, preferably from 1 mol to 3 mol, relative to 1 mol of the compound of general formula (I-D).

The process is in general carried out in a temperature range from -20°C to +120°C, preferably from +0°C to +80°C, especially at room temperature.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

Suitable solvents for the process (I-D) + (VI) → (I-B) are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, diisopropyl ether, 1,2-dimethoxyethane, dioxan or tetrahydrofuran, ethyl acetate, acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, or halogeno-hydrocarbons such as dichloromethane, dichloroethane, trichloromethane or chlorobenzene. It is also possible to use mixtures of the abovementioned solvents. Preferred for the process is acetone.

Suitable bases for the process (I-D) + (VI) → (I-B) are generally inorganic or organic bases. These preferably include alkali hydroxides, such as lithium, sodium or potassium hydroxide, alkali or alkaline-earth carbonates, such as sodium, potassium, calcium or caesium carbonate, alkali alkoxides, such as sodium or potassium methoxide, sodium or potassium ethoxide, or sodium or potassium tert.-butoxide, or cyclic amines, such as piperidine, pyridine or 4-N,N-dimethylaminopyridine, or (C_1-C_4)-trialkylamines, such as triethylamine or diisopropylethylamine, or hydrides such as sodium hydride. Preference is given to potassium carbonate. The base is employed in an amount from 0.1 mol to 10 mol, preferably from 1 mol to 3 mol, relative to 1 mol of the compound of general formula (I-D).

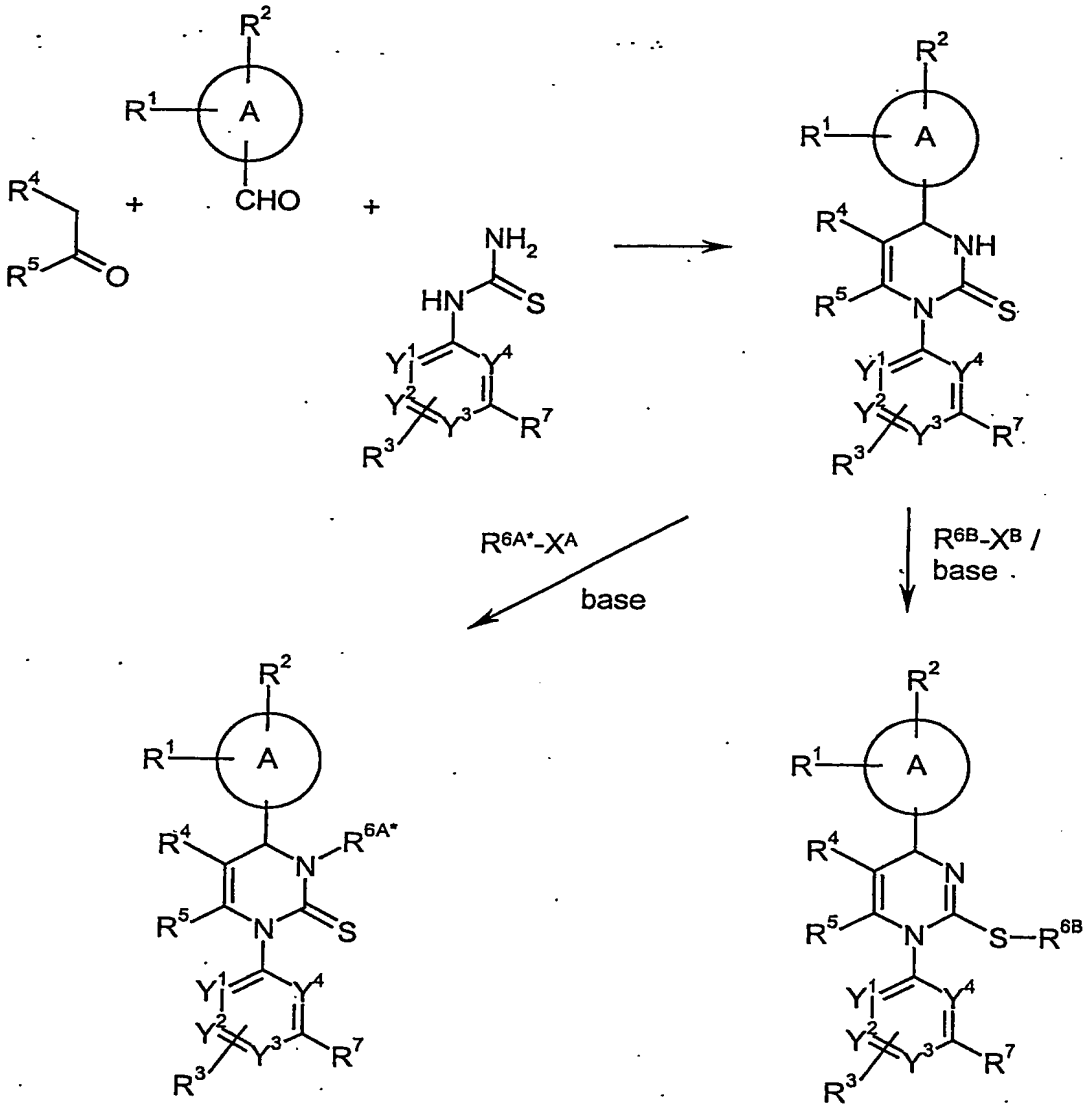
To enhance the reactivity of the compounds of general formula (VI) in cases where X^B is chloride or bromide, the process (I-D) + (VI) → (I-B) is preferably carried out in the presence of catalytic amounts of iodide sources, such as potassium iodide or tetrabutylammonium iodide.

The process is in general carried out in a temperature range from 0°C to +150°C, preferably from +0°C to +80°C, especially at room temperature.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The compounds of the general formulas (II), (III), (IV), (V) and (VI) are known per se, or they can be prepared by customary methods.

The above-mentioned method can be illustrated by the following scheme:



The compounds according to the invention exhibit an unforeseeable, useful pharmacological and pharmacokinetic activity spectrum. They are therefore suitable for use as medicaments for the treatment and/or prophylaxis of disorders in humans and animals.

Surprisingly, the compounds of the present invention show human neutrophil elastase (HNE) inhibitory activity and are therefore suitable for the preparation of medicaments for the treatment of diseases associated with HNE activity. They may thus provide an effective treatment of acute and chronic inflammatory processes, such as rheumatoid arthritis, atherosclerosis, and especially of acute and chronic pulmonary diseases, such as lung fibrosis, cystic fibrosis, pneumonia, acute respiratory distress syndrome (ARDS), in particular pulmonary emphysema, including smoking-induced emphysema, and chronic obstructive pulmonary diseases (COPD). They may also provide an effective treatment of brain trauma, cancer and other conditions in which neutrophil participation is involved.

The present invention further provides medicaments containing at least one compound according to the invention, preferably together with one or more pharmacologically safe excipient or carrier substances, and also their use for the above-mentioned purposes.

The active component can act systemically and/or locally. For this purpose, it can be applied in a suitable manner, for example orally, parenterally, pulmonally, nasally, sublingually, lingually, buccally, rectally, transdermally, conjunctivally, otically or as an implant.

For these application routes, the active component can be administered in suitable application forms.

Useful oral application forms include application forms which release the active component rapidly and/or in modified form, such as for example tablets (non-coated and coated tablets, for example with an enteric coating), capsules, sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, solutions and aerosols.

Parenteral application can be carried out with avoidance of an absorption step (intravenously, intraarterially, intracardially, intraspinally or intralumbarly) or with

inclusion of an absorption (intramuscularly, subcutaneously, intracutaneously, percutaneously or intraperitoneally). Useful parenteral application forms include injection and infusion preparations in the form of solutions, suspensions, emulsions, lyophilisates and sterile powders.

Forms suitable for other application routes include for example inhalatory pharmaceutical forms (including powder inhalers, nebulizers), nasal drops/solutions, sprays; tablets or capsules to be administered lingually, sublingually or buccally, suppositories, ear and eye preparations, vaginal capsules, aqueous suspensions (lotions, shake mixtures), lipophilic suspensions, ointments, creams, milk, pastes, dusting powders or implants.

The active components can be converted into the recited application forms in a manner known per se. This is carried out using inert non-toxic, pharmaceutically suitable excipients. These include inter alia carriers (for example microcrystalline cellulose), solvents (for example liquid polyethylene glycols), emulsifiers (for example sodium dodecyl sulphate), dispersing agents (for example polyvinylpyrrolidone), synthetic and natural biopolymers (for example albumin), stabilizers (for example antioxidants such as ascorbic acid), colorants (for example inorganic pigments such as iron oxides) or taste and/or odor corrigents.

For human use, in the case of oral administration, it is recommendable to administer doses of from 0.001 to 50 mg/kg, preferably of 0.01 mg/kg to 20 mg/kg. In the case of parenteral administration, such as, for example, intravenously or via mucous membranes nasally, buccally or inhalationally, it is recommendable to use doses of 0.001 mg/kg to 0.5 mg/kg.

In spite of this, it can be necessary in certain circumstances to depart from the amounts mentioned, namely as a function of body weight, application route, individual behaviour towards the active component, manner of preparation and time or interval at which application takes place. It can for instance be sufficient in some

cases to use less than the aforementioned minimum amount, while in other cases the upper limit mentioned will have to be exceeded. In the case of the application of larger amounts, it can be advisable to divide them into a plurality of individual doses spread through the day.

5

The percentages in the tests and examples which follows are, unless otherwise stated, by weight; parts are by weight. Solvent ratios, dilution ratios and concentrations reported for liquid/liquid solutions are each based on the volume.

A. Evaluation of physiological activity

The potential of the compounds of the invention to inhibit neutrophil elastase activity may be demonstrated, for example, using the following assays:

I. *In vitro* assays of human neutrophil elastase (HNE)

Assay contents

assay buffer: 0.1 M HEPES-NaOH buffer pH 7.4, 0.5 M NaCl, 0.1% (w/v) bovine serum albumin;

suitable concentration (see below) of HNE (18 U/mg lyophil., #20927.01, SERVA Electrophoresis GmbH, Heidelberg, Germany) in assay buffer;

suitable concentration (see below) of substrate in assay buffer;

suitable concentration of test compounds diluted with assay buffer from a 10 mM stock solution in DMSO.

Example A

***In vitro* inhibition of HNE using a fluorogenic peptide substrate (continuous read-out signal, 384 MTP assay format):**

In this protocol, the elastase substrate MeOSuc-Ala-Ala-Pro-Val-AMC (#324740, Calbiochem-Novabiochem Corporation, Merck KGaA, Darmstadt, Germany) is used. The test solution is prepared by mixing 10 µl of test compound dilution, 20 µl of HNE enzyme dilution (final concentration 8 - 0.4 µU/ml, routinely 2.1 µU/ml) and 20 µl of substrate dilution (final concentration 1 mM - 1 µM, routinely 20 µM), respectively. The solution is incubated for 0 - 2 hrs at 37°C (routinely one hour). The fluorescence of the liberated AMC due to the enzymatic reaction is measured at 37°C (TECAN spectra fluor plus plate reader). The rate of increase of the fluorescence (ex. 395 nm, em. 460 nm) is proportional to elastase activity. IC_{50} values are determined by RFU-versus-[I] plots. K_m and $K_{m(app.)}$ values are determined by Lineweaver-Burk plots and converted to K_i values by Dixon plots.

The preparation examples had IC_{50} values within the range of 5 nM - 5 µM in this assay. Representative data are given in Table 1:

Example No.	IC_{50} [nM]
1	13
3	9
4	23
6	70
7	10
9	40
12	100
14	10
15	5

Table 1

Example B

***In vitro* inhibition of HNE using a fluorogenic, unsoluble elastin substrate (discontinuous read-out signal, 96 MTP assay format):**

In this protocol the elastase substrate elastin-fluorescein (#100620, ICN Biomedicals GmbH, Eschwege, Germany) is used. The test solution is prepared by mixing 3 µl of test compound dilution, 77 µl of HNE enzyme dilution (final concentration 0.22 U/ml - 2.2 mU/ml, routinely 21.7 µU/ml) and 80 µl substrate suspension (final concentration 2 mg/ml). The suspension is incubated for 0 - 16 hrs at 37°C (routinely four hours) under slightly shaking conditions. To stop the enzymatic reaction, 160 µl of 0.1 M acetic acid are added to the test solution (final concentration 50 mM). The polymeric elastin-fluorescein is pulled down by centrifugation (Eppendorf 5804 centrifuge, 3.000 rpm, 10 min). The supernatant is transferred into a new MTP and the fluorescence of the liberated peptide fluorescein due to the enzymatic reaction is measured (BMG Fluostar plate reader). The rate of fluorescence (ex. 490 nm, em.

520 nm) is proportional to elastase activity. IC_{50} values are determined by RFU-versus-[I] plots.

II. ***In vitro* PMN elastolysis assay**

This assay is used to determine the elastolytic potential of human polymorphonuclear cells (PMNs) and assess the proportion of degradation due to neutrophil elastase [cf. Z.W. She et al., Am. J. Respir. Cell. Mol. Biol. 9, 386-392 (1993)].

Tritiated elastin, in suspension, is coated on to a 96 well plate at 10 µg per well. Test and reference [ZD-0892 (J. Med. Chem. 40, 1876-1885, 3173-3181 (1997), WO 95/21855) and α1 protease inhibitor (α1PI)] compounds are added to the wells at the appropriate concentrations. Human PMNs are separated from peripheral venous blood of healthy donors and resuspended in culture media. The neutrophils are added to the coated wells at concentrations ranging between 1 x 10^6 to 1 x 10^5 cells per well. Porcine pancreatic elastase (1.3 µM) is used as a positive control for the assay, and α1PI (1.2 µM) is used as the positive inhibitor of neutrophil elastase. The cellular control is PMNs without compound at each appropriate cell density. The cells plus compounds are incubated in a humidified incubator at 37°C for 4 hours. The plates are centrifuged to allow the harvest of cell supernatant only. The supernatant is transferred in 75 µl volumes to corresponding wells of a 96 well Lumaplate™ (solid scintillant containing plates). The plates are dried until no liquid is visible in the wells and read in a beta counter for 3 minutes per well.

Elastolysis of the ^{3}H-elastin results in an increase in counts in the supernatant. An inhibition of this elastolysis shows a decrease, from the cellular control, of tritium in the supernatant. α1PI gave 83.46 ± 3.97% (mean ± s.e.m.) inhibition at 1.2 µM (n = 3 different donors at 3.6 x 10^5 cells per well). IC_{50} values were obtained for the reference compound ZD-0892 of 45.50 ± 7.75 nM (mean ± s.e.m.) (n = 2 different donors at 3.6 x 10^5 cells per well).

Given that ZD-0892 is a selective inhibitor of PMN elastase along with the data from α1PI inhibition, these results indicate that the majority of elastin degradation by PMNs is due to the release of neutrophil elastase, and not to another elastolytic enzyme such as matrix metalloproteases (MMPs). The compounds of this invention were evaluated for their inhibitory activity in this HNE-dependent model of neutrophil elastolysis.

III. ***In vivo* model of acute lung injury in the rat**

Instillation of human neutrophil elastase (HNE) into rat lung causes acute lung damage. The extent of this injury can be assessed by measuring lung haemorrhage.

Rats are anaesthetised with Hypnorm/Hypnovel/water and instilled with HNE or saline delivered by microsprayer into the lungs. Test compounds are administered by intravenous injection, by oral gavage or by inhalation at set times prior to the administration of HNE. Sixty minutes after the administration of elastase animals are killed by an anaesthetic overdose (sodium pentobarbitone) and the lungs lavaged with 2 ml heparinised phosphate buffered saline (PBS). Bronchoalveolar lavage (BAL) volume is recorded and the samples kept on ice. Each BAL sample is centrifuged at 900 r.p.m. for 10 minutes at 4-10°C. The supernatant is discarded and the cell pellet resuspended in PBS and the sample spun down again. The supernatant is again discarded and the cell pellet resuspended in 1 ml 0.1% cetyltrimethylammonium bromide (CTAB) / PBS to lyse the cells. Samples are frozen until blood content is assayed. Prior to the haemorrhage assay the samples are defrosted and mixed. 100 µl of each sample are placed into a separate well of a 96 well flat-bottomed plate. All samples are tested in duplicate. 100 µl 0.1% CTAB/PBS is included as a blank. The absorbance of the well contents is measured at 415 nm using a spectrophotometer. A standard curve is constructed by measuring the OD at 415 nm of different concentrations of blood in 0.1% CTAB/PBS. Blood content values are calculated by comparison to the standard curve (included in each plate) and normalised for the volume of BAL fluid retrieved.

The compounds of this invention were evaluated intravenously, orally or by inhalation for their inhibitory activity in this model of HNE-induced haemorrhage in the rat.

B. Examples

Abbreviations:

DMSO	dimethylsulfoxide
ESI	electro-spray ionisation (for MS)
HPLC	high pressure liquid chromatography
LC-MS	liquid chromatography coupled with mass spectroscopy
MS	mass spectroscopy
NMR	nuclear magnetic resonance
of th.	of theoretical (yield)
R_t	retention time (for HPLC)
THF	tetrahydrofuran

General methods:

All reactions were carried out under an argon atmosphere unless otherwise noted. Solvents were used as purchased from commercial sources without further purification. 'Silica gel' or 'Silica' refers to Silica gel 60 (0.040 mm-0.063 mm) from Merck KGaA company, Germany. Compounds purified over preparative HPLC were purified over a RP18-column with acetonitrile and water as the eluent, using a 1:9 to 9:1 gradient.

LC-MS and HPLC methods:

Method 1:

Instrument: Micromass Platform LCZ, HP1100; Column: Symmetry C18, 50 mm x 2.1 mm, 3.5 µm; Eluent A: water + 0.05% formic acid, Eluent B: acetonitrile + 0.05% formic acid; Gradient: 0.0 min 90% A → 4.0 min 10% A → 6.0 min 10% A; Oven: 40°C; Flow: 0.5 ml/min; UV-detection: 208-400 nm

Method 2:

Instrument MS: Micromass ZQ; Instrument HPLC: Waters Alliance 2790; Column: UPTISPHERE HDO, 50 mm x 2.0 mm, 3.0 µm; Eluent A: water + 0.05% formic acid, Eluent B: acetonitrile + 0.05% formic acid; Gradient: 0.0 min 5% B → 2.0 min 40% B → 4.5 min 90% B → 5.5 min 90% B; Temperature: 45°C; Flow: 0.75 ml/min; UV-detection: 210 nm

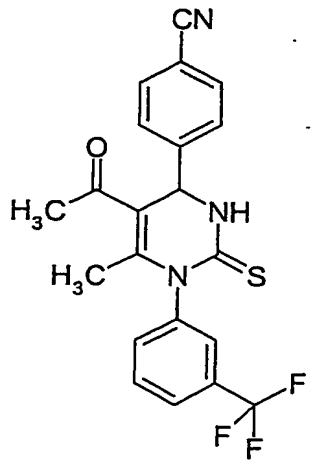
Method 3:

Instrument: Micromass Platform LCZ, HP1100; Column: Grom-SIL120 ODS-4 HE, 50 mm x 2.0 mm, 3 µm; Eluent A: water + 0.05% formic acid, Eluent B: acetonitrile + 0.05% formic acid; Gradient: 0.0 min 100% A → 0.2 min 100% A → 2.9 min 30% A → 3.1 min 10% A → 4.5 min 10% A; Temperature: 55°C; Flow: 0.8 ml/min; UV-detection: 208-400 nm.

Preparation Examples:

Example 1

4-{5-Acetyl-6-methyl-2-thioxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-4-pyrimidinyl}benzonitrile



3-Trifluoromethylphenyl thiourea (200 mg, 0.91 mmol), 4-cyanobenzaldehyde (238.2 mg, 1.82 mmol) and 2,4-pentanedione (181.9 mg, 1.82 mmol) are dissolved in 5 ml THF. Ethyl polyphosphate (0.30 g) is added and the reaction mixture is stirred at reflux temperature overnight. After cooling to room temperature, the reaction is quenched with 10 ml of water and extracted with 10 ml ethyl acetate (2 x). The combined organic layers are dried with sodium sulfate and the solvent is removed *in vacuo*. The product is purified via preparative HPLC (RP18-column; eluent: acetonitrile-water, gradient 10:90 to 90:10).

Yield: 53 mg (14% of th.)

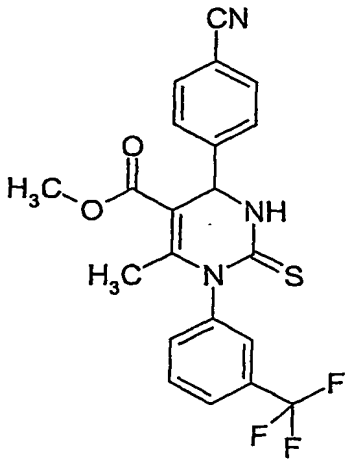
LC-MS (method 1): $R_t = 4.48$ min.

MS (ESIpos): $m/z = 416$ $(M+H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): $\delta = 10.32$ (d, 1H); 7.93 (d, 2H); 7.43-7.84 (m, 6H); 5.48 (d, 1H); 2.26 (s, 3H); 1.99 (s, 3H) ppm.

Example 2

Methyl 4-(4-cyanophenyl)-6-methyl-2-thioxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate



3-Trifluoromethylphenyl thiourea (200 mg, 0.91 mmol), 4-cyanobenzaldehyde (238.2 mg, 1.82 mmol) and methyl acetoacetate (211 mg, 1.82 mmol) are dissolved in 5 ml THF. Ethyl polyphosphate (0.30 g) is added and the reaction mixture is stirred at reflux temperature overnight. After cooling to room temperature, the reaction is quenched with 10 ml of water and extracted with 10 ml ethyl acetate (2 x). The combined organic layers are dried with sodium sulfate and the solvent is removed *in vacuo*. The product is purified via preparative HPLC (RP18-column; eluent: acetonitrile-water, gradient 10:90 to 90:10).

Yield: 315 mg (80% of th.)

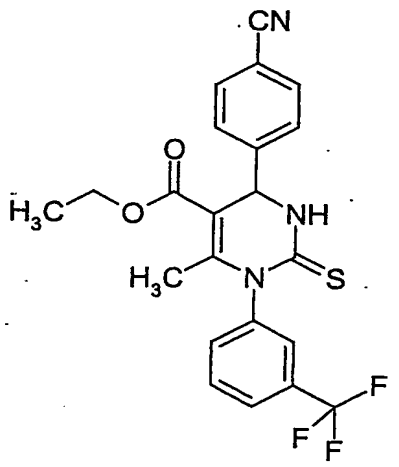
LC-MS (method 1): $R_t = 4.70$ min.

MS (ESIpos): $m/z = 432$ $(M+H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): $\delta = 10.24$ (d, 1H); 7.92 (d, 2H); 7.54-7.83 (m, 6H); 5.40 (d, 1H); 3.63 (s, 3H); 2.06 (s, 3H) ppm.

Example 3

Ethyl 4-(4-cyanophenyl)-6-methyl-2-thioxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate



3-Trifluoromethylphenyl thiourea (3.00 g, 13.6 mmol), 4-cyanobenzaldehyde (3.57 g, 27.3 mmol) and ethyl acetoacetate (3.55 g, 27.3 mmol) are dissolved in

50 ml THF. Ethyl polyphosphate (4.50 g) is added and the reaction mixture is stirred at reflux temperature overnight. After cooling to room temperature, it is quenched with 50 ml of water and extracted with 100 ml ethyl acetate (2 x). The combined organic layers are dried with sodium sulfate and the solvent is removed *in vacuo*. The product is purified via preparative HPLC (RP18-column; eluent: acetonitrile-water, gradient 10:90 to 90:10).

Yield: 3.15 g (52% of th.)

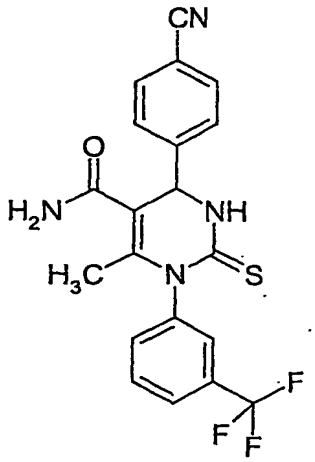
LC-MS (method 2): $R_t = 4.10$ min.

MS (ESIpos): $m/z = 446$ $(M+H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 10.18 (d, 1H); 7.92 (d, 2H); 7.45-7.82 (m, 6H); 5.40 (d, 1H); 4.08 (q, 2H); 2.05 (s, 3H); 1.12 (t, 3H) ppm.

Example 4

4-(4-Cyanophenyl)-6-methyl-2-thioxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



3-Trifluoromethylphenyl thiourea (200 mg, 0.91 mmol), 4-cyanobenzaldehyde (238.2 mg, 1.82 mmol) and 3-oxobutanamide (183 mg, 1.82 mmol) are dissolved in 5 ml THF. Ethyl polyphosphate (0.30 g) is added and the reaction mixture is stirred at reflux temperature overnight. After cooling to room temperature, it is quenched

with 10 ml of water and extracted with 10 ml ethyl acetate (2 x). The combined organic layers are dried with sodium sulfate and the solvent is removed *in vacuo*. The product is purified via preparative HPLC (RP18-column; eluent: acetonitrile-water, gradient 10:90 to 90:10).

Yield: 29 mg (8% of th.)

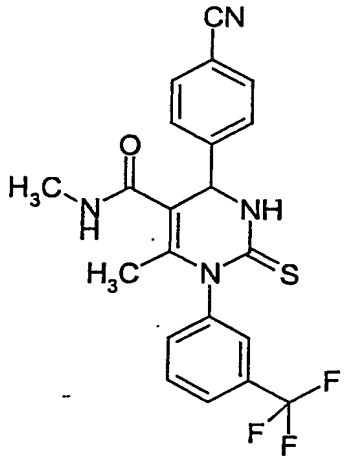
LC-MS (method 1): $R_t = 4.35$ min.

MS (ESIpos): $m/z = 417$ $(M+H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): $\delta = 9.86$ (d, 1H); 7.93 (d, 2H); 7.76 (d, 1H); 7.67 (t, 1H); 7.24-7.62 (m, 4H); 7.59 (d, 2H); 5.40 (d, 1H); 1.74 (s, 3H) ppm.

Example 5

4-(4-Cyanophenyl)-N,6-dimethyl-2-thioxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



3-Trifluoromethylphenyl thiourea (200 mg, 0.91 mmol), 4-cyanobenzaldehyde (238.2 mg, 1.82 mmol) and N-methyl-3-oxobutanamide (299 mg, 1.82 mmol) are dissolved in 5 ml THF. Ethyl polyphosphate (0.30 g) is added and the reaction mixture is stirred at reflux temperature overnight. After cooling to room temperature, the reaction is quenched with 10 ml of water and extracted with 10 ml ethyl acetate (2 x). The combined organic layers are dried with sodium sulfate and the solvent is

removed *in vacuo*. The product is purified via preparative HPLC (RP18-column; eluent: acetonitrile-water, gradient 10:90 to 90:10).

Yield: 104 mg (27% of th.)

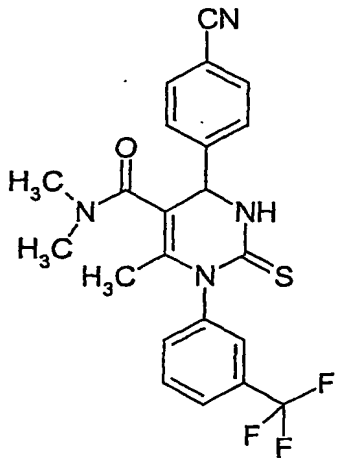
LC-MS (method 1): R_t = 4.10 min.

MS (ESIpos): m/z = 431 $(M+H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 9.89 (d, 1H); 7.93 (d, 2H); 7.54 (d, 2H); 7.38-8.12 (m, 5H); 5.36 (d, 1H); 2.59 (d, 3H); 1.66 (s, 3H) ppm.

Example 6

4-(4-Cyanophenyl)-N,N,6-trimethyl-2-thioxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



3-Trifluoromethylphenyl thiourea (200 mg, 0.91 mmol), 4-cyanobenzaldehyde (238.2 mg, 1.82 mmol) and N,N-dimethyl-3-oxobutanamide (235 mg, 1.82 mmol) are dissolved in 5 ml THF. Ethyl polyphosphate (0.30 g) is added and the reaction mixture is stirred at reflux temperature overnight. After cooling to room temperature, it is quenched with 10 ml of water and extracted with 10 ml ethyl acetate (2 x). The combined organic layers are dried with sodium sulfate and the solvent is removed *in vacuo*. The product is purified via preparative HPLC (RP18-column; eluent: acetonitrile-water, gradient 10:90 to 90:10).

Yield: 270 mg (67% of th.)

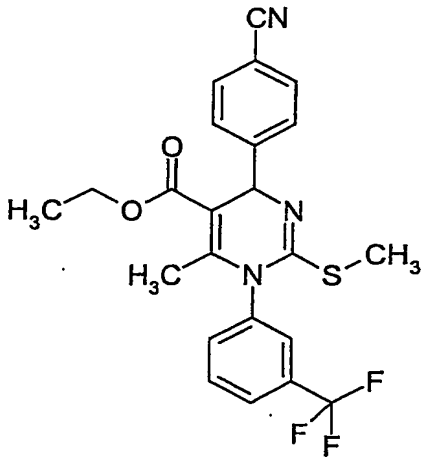
LC-MS (method 1): $R_t = 4.20$ min.

MS (ESIpos): m/z = 445 $(M+H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): $\delta = 9.77$ (d, 1H); 7.92 (d, 2H); 7.54 (d, 2H); 7.49-7.83 (m, 4H); 5.19 (br. s, 1H); 3.33 (s, 3H); 2.78 (s, 3H); 1.43 (s, 3H) ppm.

Example 7

Ethyl 4-(4-cyanophenyl)-6-methyl-2-(methylsulfanyl)-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-5-pyrimidinecarboxylate



Ethyl 4-(4-cyanophenyl)-6-methyl-2-thioxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (Example 3; 1000 mg, 2.24 mmol), iodomethane (350.5 mg, 2.47 mmol) and potassium carbonate (341 mg, 1.82 mmol) are dissolved in 20 ml acetone and stirred at room temperature overnight. The solvent is removed *in vacuo* and the product is purified by column chromatography (silica gel; eluent: cyclohexane-ethyl acetate, gradient 90:10 to 50:50).

Yield: 998 mg (97% of th.)

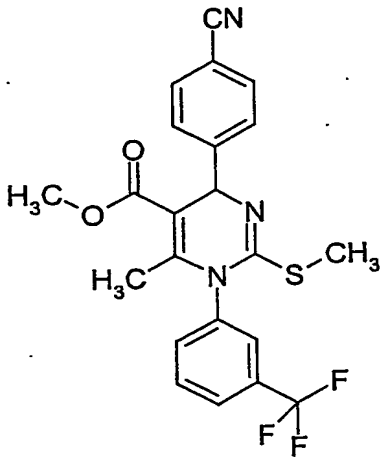
LC-MS (method 3): $R_t = 4.20$ min.

MS (ESIpos): m/z = 460 $(M+H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 7.85 (d, 2H); 7.69-7.94 (m, 4H); 7.60 (d, 2H); 5.76 (s, 1H); 4.04 (q, 2H); 2.14 (s, 3H); 2.01 (s, 3H); 1.11 (t, 3H) ppm.

Example 8

Methyl 4-(4-cyanophenyl)-6-methyl-2-(methylsulfanyl)-1-[3-(trifluoromethyl)-phenyl]-1,4-dihydro-5-pyrimidinecarboxylate



Ethyl 4-(4-cyanophenyl)-6-methyl-2-(methylsulfanyl)-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-5-pyrimidinecarboxylate (Example 7; 100 mg, 0.22 mmol) and sodium methoxide (117.6 mg, 2.18 mmol) are dissolved in 5 ml methanol and stirred at reflux temperature for 3 h. The reaction is quenched with 10 ml of water and the aqueous phase is extracted with 10 ml methylene chloride (2 x). After drying with sodium sulfate, the solvent is removed *in vacuo* and the product is purified by column chromatography (silica gel; eluent: cyclohexane-ethyl acetate, gradient 90:10 to 50:50).

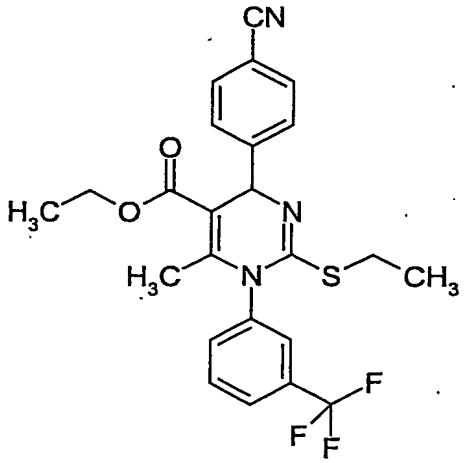
Yield: 60 mg (62% of th.)

LC-MS (method 2): R_t = 4.27 min.

MS (ESIpos): m/z = 446 $(M+H)^+$.

Example 9

Ethyl 4-(4-cyanophenyl)-6-methyl-2-(ethylsulfanyl)-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-5-pyrimidinecarboxylate



Ethyl 4-(4-cyanophenyl)-6-methyl-2-thioxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (Example 3; 100 mg, 0.22 mmol), iodoethane (38.5 mg, 0.25 mmol) and potassium carbonate (34.1 mg, 0.25 mmol) are dissolved in 3 ml acetone and stirred at room temperature overnight. The solvent is removed *in vacuo* and the product is purified via preparative HPLC (RP18-column; eluent: acetonitrile-water, gradient 10:90 to 90:10).

Yield: 62 mg (58% of th.)

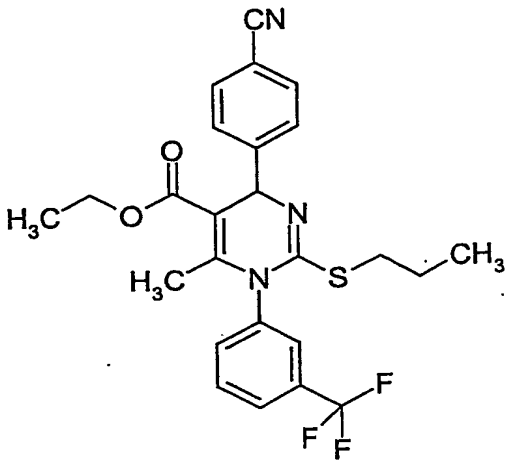
LC-MS (method 2): $R_t = 4.67$ min.

MS (ESIpos): $m/z = 474$ $(M+H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): $\delta = 7.85$ (d, 2H); 7.68-7.94 (m, 4H); 7.60 (d, 2H); 5.75 (s, 1H); 4.03 (q, 2H); 2.74 (m, 2H); 2.01 (s, 3H); 1.11 (t, 3H); 1.01 (t, 3H) ppm.

Example 10

Ethyl 4-(4-cyanophenyl)-6-methyl-2-(propylsulfanyl)-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-5-pyrimidinecarboxylate



Ethyl 4-(4-cyanophenyl)-6-methyl-2-thioxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (Example 3; 100 mg, 0.22 mmol), 1-iodopropane (42.0 mg, 0.25 mmol) and potassium carbonate (34.1 mg, 0.25 mmol) are dissolved in 3 ml acetone and stirred at room temperature overnight. The solvent is removed *in vacuo* and the product is purified via preparative HPLC (RP18-column; eluent: acetonitrile-water, gradient 10:90 to 90:10).

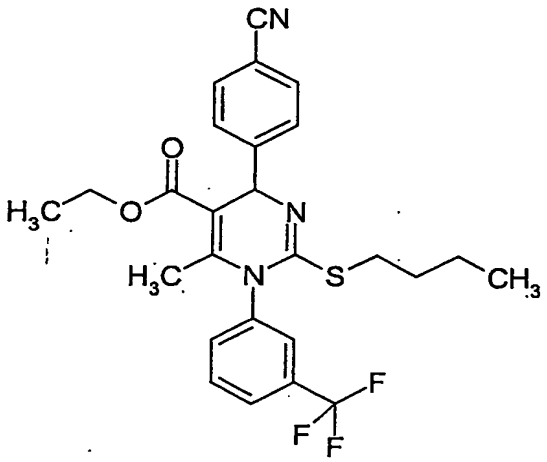
Yield: 45 mg (41% of th.)

LC-MS (method 3): $R_t = 4.45$ min.

MS (ESIpos): $m/z = 488$ $(M+H)^+$.

Example 11

Ethyl 4-(4-cyanophenyl)-6-methyl-2-(butylsulfanyl)-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-5-pyrimidinecarboxylate



Ethyl 4-(4-cyanophenyl)-6-methyl-2-thioxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (Example 3; 100 mg, 0.22 mmol), 1-iodobutane (45.0 mg, 0.25 mmol) and potassium carbonate (34.1 mg, 0.25 mmol) are dissolved in 3 ml acetone and stirred at room temperature overnight. The solvent is removed *in vacuo* and the product is purified via preparative HPLC (RP18-column; eluent: acetonitrile-water, gradient 10:90 to 90:10).

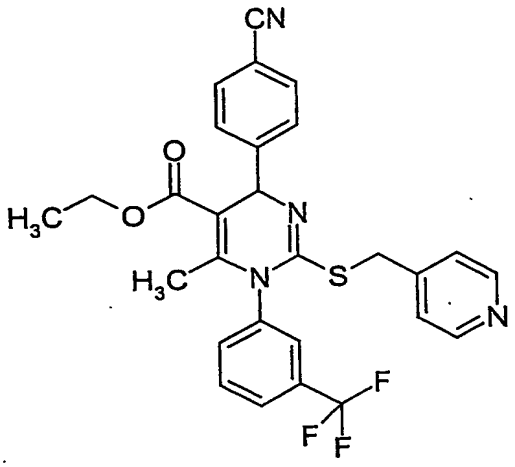
Yield: 53 mg (47% of th.)

LC-MS (method 3): $R_t = 4.58$ min.

MS (ESIpos): $m/z = 402$ $(M+H)^+$.

Example 12

Ethyl 4-(4-cyanophenyl)-6-methyl-2-[(4-pyridinylmethyl)sulfanyl]-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-5-pyrimidinecarboxylate



Ethyl 4-(4-cyanophenyl)-6-methyl-2-thioxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (Example 3; 100 mg, 0.22 mmol), 4-(bromomethyl)pyridine hydrobromide (62.5 mg, 0.25 mmol), N,N,N-tributyl-1-butanaminium iodide (7 mg, 0.03 mmol) and potassium carbonate (65.2 mg, 0.47 mmol) are dissolved in 3 ml acetone and stirred at room temperature overnight. The solvent is removed *in vacuo* and the product is purified via preparative HPLC (RP18-column; eluent: acetonitrile-water, gradient 10:90 to 90:10).

Yield: 34 mg (28% of th.)

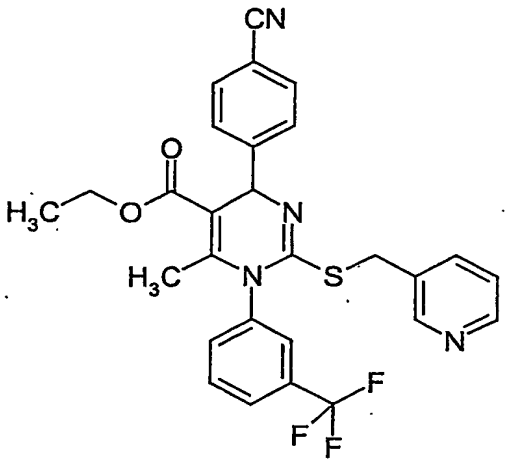
LC-MS (method 3): $R_t = 3.92$ min.

MS (ESIpos): $m/z = 537$ $(M+H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): $\delta = 8.34$ (m, 2H); 7.89 (m, 2H); 7.82 (d, 2H); 7.72 (m, 2H); 7.57 (d, 2H); 7.53 (m, 1H); 7.13 (dd, 1H); 5.78 (s,1H); 3.94-4.14 (m, 4H); 2.00 (s, 3H); 1.10 (t, 3H) ppm.

Example 13

Ethyl 4-(4-cyanophenyl)-6-methyl-2-[(3-pyridinylmethyl)sulfanyl]-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-5-pyrimidinecarboxylate



Ethyl 4-(4-cyanophenyl)-6-methyl-2-thioxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (Example 3; 100 mg, 0.22 mmol), 3-(chloromethyl)pyridine hydrochloride (40.5 mg, 0.25 mmol), N,N,N-tributyl-1-butanaminium iodide (7 mg, 0.03 mmol) and potassium carbonate (65.2 mg, 0.47 mmol) are dissolved in 3 ml acetone and stirred at room temperature overnight. The solvent is removed *in vacuo* and the product is purified via preparative HPLC (RP18-column; eluent: acetonitrile-water, gradient 10:90 to 90:10).

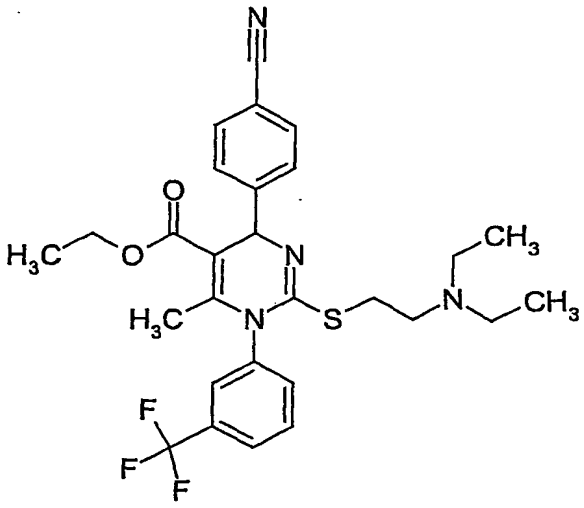
Yield: 25 mg (21% of th.)

LC-MS (method 2): $R_t = 3.93$ min.

MS (ESIpos): $m/z = 537$ $(M+H)^+$.

Example 14

Ethyl 4-(4-cyanophenyl)-2-{[2-(diethylamino)ethyl]sulfanyl}-6-methyl-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-5-pyrimidinecarboxylate



Ethyl 4-(4-cyanophenyl)-6-methyl-2-thioxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (Example 3; 100 mg, 0.22 mmol), N-(2-bromoethyl)-N,N-diethylamine hydrobromide (64.5 mg, 0.25 mmol), N,N,N-tributyl-1-butanaminium iodide (7 mg, 0.03 mmol) and potassium carbonate (65.2 mg, 0.47 mmol) are dissolved in 3 ml acetone and stirred at room temperature overnight. The solvent is removed *in vacuo* and the product is purified via preparative HPLC (RP18-column; eluent: acetonitrile-water, gradient 10:90 to 90:10).

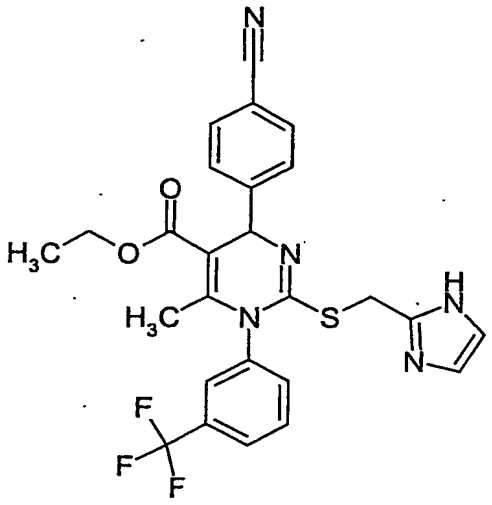
Yield: 15 mg (12% of th.)

LC-MS (method 2): $R_t = 3.17$ min.

MS (ESIpos): $m/z = 545$ $(M+H)^+$.

Example 15

Ethyl 4-(4-cyanophenyl)-2-[(1H-imidazol-2-ylmethyl)sulfanyl]-6-methyl-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-5-pyrimidinecarboxylate



Ethyl 4-(4-cyanophenyl)-6-methyl-2-thioxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (Example 3; 100 mg, 0.22 mmol), 2-(bromomethyl)-1H-imidazole hydrobromide (64.5 mg, 0.25 mmol), N,N,N-tributyl-1-butanaminium iodide (7 mg, 0.03 mmol) and potassium carbonate (65.2 mg, 0.47 mmol) are dissolved in 3 ml acetone and stirred at room temperature overnight. The solvent is removed by distillation *in vacuo* and the product is purified via preparative HPLC (RP18-column; eluent: acetonitrile-water, gradient 10:90 to 90:10).

Yield: 13 mg (11% of th.)

LC-MS (method 3): $R_t = 3.74$ min.

MS (ESIpos): m/z = 526 $(M+H)^+$.

C. Operative examples relating to pharmaceutical compositions

The compounds according to the invention can be converted into pharmaceutical preparations as follows:

Tablet:

Composition:

100 mg of the compound of Example 1, 50 mg of lactose (monohydrate), 50 mg of maize starch (native), 10 mg of polyvinylpyrrolidone (PVP 25) (from BASF, Ludwigshafen, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg, diameter 8 mm, curvature radius 12 mm.

Preparation:

The mixture of active component, lactose and starch is granulated with a 5% solution (m/m) of the PVP in water. After drying, the granules are mixed with magnesium stearate for 5 min. This mixture is moulded using a customary tablet press (tablet format, see above). The moulding force applied is typically 15 kN.

Orally administrable suspension:

Composition:

1000 mg of the compound of Example 1, 1000 mg of ethanol (96%), 400 mg of Rhodigel (xanthan gum from FMC, Pennsylvania, USA) and 99 g of water.

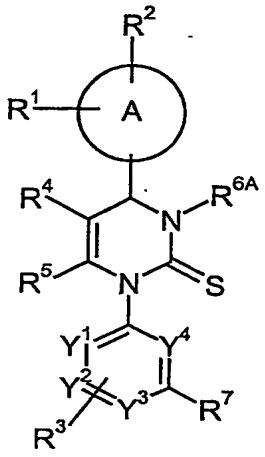
A single dose of 100 mg of the compound according to the invention is provided by 10 ml of oral suspension.

Preparation:

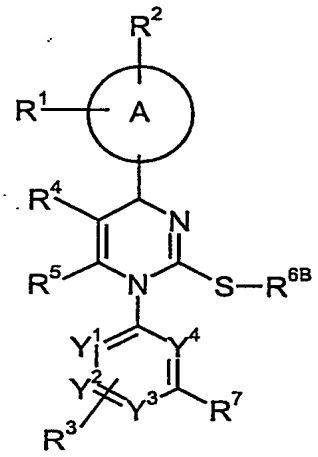
The Rhodigel is suspended in ethanol and the active component is added to the suspension. The water is added with stirring. Stirring is continued for about 6h until the swelling of the Rhodigel is complete.

We claim

1. Compounds of the general formulas (I-A) and (I-B)



(I-A)



(I-B),

wherein

A represents an aryl or heteroaryl ring,

R^1, R^2 and R^3 independently from each other represent hydrogen, halogen, nitro, cyano, C_1-C_6-alkyl, hydroxy or C_1-C_6-alkoxy, wherein C_1-C_6-alkyl and C_1-C_6-alkoxy can be further substituted with one to three identical or different radicals selected from the group consisting of halogen, hydroxy and C_1-C_4-alkoxy,

R^4 represents C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, hydroxycarbonyl, aminocarbonyl, mono- or di-C_1-C_4-alkylaminocarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylcarbonyl, heterocyclylcarbonyl, heteroaryl, heterocyclyl or cyano, wherein C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, mono- and di-C_1-C_4-alkylaminocarbonyl can be further substituted with one to three identical or different radicals selected from the group consisting of C_3-C_8-cycloalkyl, hydroxy, C_1-

C_4-alkoxy, C_1-C_4-alkoxycarbonyl, hydroxycarbonyl, aminocarbonyl, mono- and di-C_1-C_4-alkylaminocarbonyl, C_1-C_4-alkylcarbonylamino, amino, mono- and di-C_1-C_4-alkylamino, heteroaryl, heterocyclyl and tri-(C_1-C_6-alkyl)-silyl,

R^5 represents C_1-C_4-alkyl, which can be substituted with one to three identical or different radicals selected from the group consisting of halogen, hydroxy, C_1-C_6-alkoxy, C_1-C_6-alkenoxy, C_1-C_6-alkylthio, amino, mono- and di-C_1-C_6-alkylamino, arylamino, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl and the radical -O-C_1-C_4-alkyl-O-C_1-C_4-alkyl,

R^{6A} represents hydrogen, C_1-C_6-alkylcarbonyl, C_3-C_8-cycloalkylcarbonyl, C_1-C_6-alkoxycarbonyl, mono- or di-C_1-C_4-alkylaminocarbonyl, wherein C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, mono- and di-C_1-C_4-alkylaminocarbonyl can be substituted with one to three identical or different radicals selected from the group consisting of C_3-C_8-cycloalkyl, hydroxy, C_1-C_4-alkoxy, amino, mono- and di-C_1-C_4-alkylamino,

R^{6B} represents C_1-C_6-alkyl, which can be substituted with one to three identical or different radicals selected from the group consisting of hydroxy, C_1-C_4-alkoxy, amino, mono- and di-C_1-C_4-alkylamino, aryl and heteroaryl,

R^7 represents halogen, nitro, cyano, C_1-C_6-alkyl, hydroxy or C_1-C_6-alkoxy, wherein C_1-C_6-alkyl and C_1-C_6-alkoxy can be further substituted with one to three identical or different radicals selected from the group consisting of halogen, hydroxy and C_1-C_4-alkoxy,

and

Y^1, Y^2, Y^3 and Y^4 independently from each other represent CH or N, wherein the ring contains either 0, 1 or 2 nitrogen atoms.

2. Compounds of general formulas (I-A) and (I-B) according to Claim1, wherein

A represents a phenyl or pyridyl ring,

R^1, R^2 and R^3 independently from each other represent hydrogen, fluoro, chloro, bromo, nitro, cyano, methyl, ethyl, trifluoromethyl or trifluoromethoxy,

R^4 represents C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, hydroxycarbonyl, aminocarbonyl, mono- or di-C_1-C_4-alkylaminocarbonyl or cyano, wherein C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl and mono-C_1-C_4-alkylaminocarbonyl can be substituted with one to three identical or different radicals selected from the group consisting of C_3-C_6-cycloalkyl, hydroxy, C_1-C_4-alkoxy, C_1-C_4-alkoxycarbonyl, amino, mono- or di-C_1-C_4-alkylamino, heteroaryl and heterocyclyl,

R^5 represents methyl or ethyl,

R^{6A} represents hydrogen, C_1-C_6-alkylcarbonyl or C_3-C_6-cycloalkylcarbonyl, wherein C_1-C_6-alkylcarbonyl can be substituted with a radical selected from the group consisting of C_3-C_6-cycloalkyl, hydroxy, C_1-C_4-alkoxy, amino, mono- and di-C_1-C_4-alkylamino,

R^{6B} represents C_1-C_6-alkyl, which can be substituted with a radical selected from the group consisting of hydroxy, C_1-C_4-alkoxy, amino, mono- and di-C_1-C_4-alkylamino, phenyl and heteroaryl,

R^7 represents halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, methyl or ethyl,

and

Y^1, Y^2, Y^3 and Y^4 each represent CH.

3. Compounds of general formulas (I-A) and (I-B) according to Claim 1 or 2, wherein

A represents a phenyl or a pyridyl ring,

R^1 and R^3 each represent hydrogen,

R^2 represents fluoro, chloro, bromo, nitro or cyano,

R^4 represents C_1-C_4-alkylcarbonyl or C_1-C_4-alkoxycarbonyl, wherein C_1-C_4-alkoxycarbonyl can be substituted with a radical selected from the group consisting of hydroxy, C_1-C_4-alkoxy, C_1-C_4-alkoxycarbonyl, mono- and di-C_1-C_4-alkylamino, heteroaryl and heterocyclyl,

R^5 represents methyl,

R^{6A} represents hydrogen, C_1-C_6-alkylcarbonyl or C_3-C_6-cycloalkyl-carbonyl,

R^{6B} represents C_1-C_4-alkyl, which can be substituted with a radical selected from the group consisting of hydroxy, C_1-C_4-alkoxy, amino, di-C_1-C_4-alkylamino, phenyl, pyridyl and imidazolyl,

R^7 represents trifluoromethyl or nitro,

and

Y^1, Y^2, Y^3 and Y^4 each represent CH.

4. Compounds of general formulas (I-A) and (I-B) according to at least one of Claims 1 to 3, wherein A is phenyl or pyridyl.

5. Compounds of general formulas (I-A) and (I-B) according to at least one of Claims 1 to 4, wherein R^1 is hydrogen.

6. Compounds of general formulas (I-A) and (I-B) according to at least one of Claims 1 to 5, wherein R^2 is cyano.

7. Compounds of general formulas (I-A) and (I-B) according to at least one of Claims 1 to 6, wherein R^3 is hydrogen.

8. Compounds of general formulas (I-A) and (I-B) according to at least one of Claims 1 to 7, wherein R^4 is C_1-C_4-alkoxycarbonyl or C_1-C_4-alkylcarbonyl.

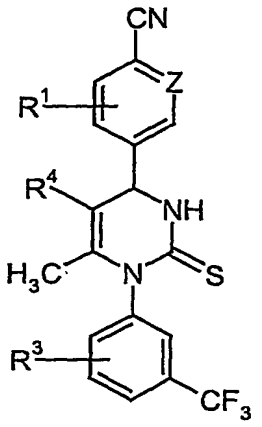
9. Compounds of general formulas (I-A) and (I-B) according to at least one of Claims 1 to 8, wherein R^5 is methyl.

10. Compounds of general formulas (I-A) and (I-B) according to at least one of Claims 1 to 9, wherein R^7 is trifluoromethyl or nitro.

11. Compounds of general formula (I-A) according to at least one of Claims 1 to 10, wherein R^{6A} is hydrogen.

12. Compounds of general formula (I-B) according to at least one of Claims 1 to 10, wherein R^{6B} is methyl, (1H-imidazol-2-yl)methyl or 2-(diethylamino)-ethyl.

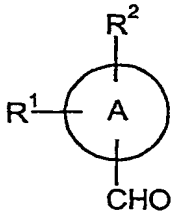
13. Compounds of general formula (I-C)



(I-C),

wherein Z represents CH or N, and R^1, R^3 and R^4 have the meaning indicated in Claims 1 to 11.

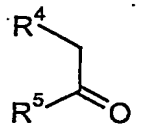
14. Process for synthesizing the compounds of general formulas (I-A), (I-B) or (I-C), respectively, as defined in Claims 1 to 13, by condensing compounds of general formula (II)



(II),

wherein A, R^1 and R^2 have the meaning indicated in Claims 1 to 13,

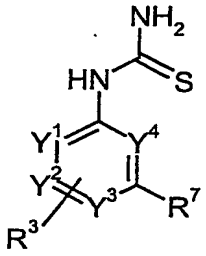
with compounds of general formula (III)



(III),

wherein R^4 and R^5 have the meaning indicated in Claims 1 to 13,

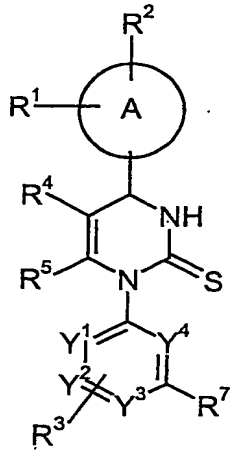
and compounds of general formula (IV)



(IV),

wherein R^3, R^7, and Y^1 to Y^4 have the meaning indicated in Claims 1 to 13,

in the presence of an acid either in a three-component / one-step reaction or sequentially to give compounds of the general formula (I-D)



(I-D),

wherein A, R^1 to R^5, R^7, and Y^1 to Y^4 have the meaning indicated in Claims 1 to 13,

optionally followed by reaction of the compounds of general formula (I-D) in the presence of a base either

[A] with compounds of the general formula (V)

$$R^{6A*}–X^A \quad (V),$$

wherein R^{6A*} has the meaning of R^{6A} as indicated in Claims 1 to 13, but does not represent hydrogen, and X^A represents a leaving group, such as halogen,

to give compounds of the general formula (I-A),

or

[B] with compounds of the general formula (VI)

$$R^{6B}–X^B \quad (VI),$$

wherein R^{6B} has the meaning indicated in Claims 1 to 13, and X^B represents a leaving group, such as halogen, tosylate, mesylate or sulfate,

to give compounds of the general formula (I-B).

15. The composition containing at least one compound of general formula (I-A) or (I-C), as defined in Claims 1 to 11 and 13, and a pharmacologically acceptable diluent.

16. A composition according to Claim 15 for the treatment of acute and chronic inflammatory processes.

17. The process for the preparation of compositions according to Claim 15 and 16 characterized in that the compounds of general formula (I-A) or (I-C), as defined in Claims 1 to 11 and 13, together with customary auxiliaries are brought into a suitable application form.

18. Use of the compounds of general formula (I-A) or (I-C), as defined in Claims 1 to 11 and 13, for the preparation of medicaments.

19. Use according to Claim 18 for the preparation of medicaments for the treatment of acute and chronic inflammatory processes.

20. Use according to Claim 19, wherein the process is chronic obstructive pulmonary disease.

21. The composition containing at least one compound of general formula (I-B), as defined in Claims 1 to 10 and 12, and a pharmacologically acceptable diluent.

22. A composition according to Claim 21 for the treatment of acute and chronic inflammatory processes.

23. The process for the preparation of compositions according to Claim 21 and 22 characterized in that the compounds of general formula (I-B), as defined in Claims 1 to 10 and 12, together with customary auxiliaries are brought into a suitable application form.

24. Use of the compounds of general formula (I-B), as defined in Claims 1 to 10 and 12, for the preparation of medicaments.

25. Use according to Claim 24 for the preparation of medicaments for the treatment of acute and chronic inflammatory processes.

26. Use according to Claim 25, wherein the process is chronic obstructive pulmonary disease.

27. Process for controlling chronic obstructive pulmonary disease in humans and animals by administration of a neutrophil elastase inhibitory amount of at least one compound according to any of Claims 1 to 13.

Heterocyclic derivatives

Abstract

The invention relates to novel heterocyclic derivatives, processes for their preparation, and their use in medicaments, especially for the treatment of chronic obstructive pulmonary diseases.